original article

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Lack of prophylaxis before the onset of acute venous thromboembolism among hospitalized cancer patients: the SWIss Venous ThromboEmbolism Registry (SWIVTER)

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Background: Venous thromboembolism (VTE) prophylaxis remains underutilized, particularly in cancer patients. We explored clinical predictors of prophylaxis in hospitalized cancer patients before the onset of acute VTE.
Methods: In the SWiss Venous ThromboEmbolism Registry, 257 cancer patients (61 ± 15 years) with acute VTE and prior hospitalization for acute medical illness or surgery within 30 days (91% were at high risk with Geneva VTE risk score ≥3) were enrolled.
Results: Overall, 153 (60%) patients received prophylaxis (49% pharmacological and 21% mechanical) before the onset of acute VTE. Outpatient status at the time of VTE diagnosis [odds ratio (OR) 0.31, 95% confidence interval (CI) 0.18–0.53], ongoing chemotherapy (OR 0.51, 95% CI 0.31–0.85), and recent chemotherapy (OR 0.53, 95% CI 0.32–0.88) were univariately associated with the absence of VTE prophylaxis. In multivariate analysis, intensive care unit admission within 30 days (OR 7.02, 95% CI 2.38–20.64), prior deep vein thrombosis (OR 3.48, 95% CI 2.14–5.64), surgery within 30 days (OR 2.43, 95% CI 1.19–4.99), bed rest >3 days (OR 2.02, 95% CI 1.08–3.78), and outpatient status (OR 0.38, 95% CI 0.19–0.76) remained the only independent predictors of thromboprophylaxis.
Conclusions: Although most hospitalized cancer patients were at high risk, 40% did not receive any prophylaxis before the onset of acute VTE. There is a need to improve thromboprophylaxis in cancer patients, particularly in the presence of recent or ongoing chemotherapy.
Key words: cancer, thromboprophylaxis, venous thromboembolism

introduction

Patients with cancer have a sixfold increased risk of venous thromboembolism (VTE) compared with those without cancer [1, 2]. VTE remains the second leading cause of death among cancer patients [3] and the first leading cause of death in patients with cancer receiving outpatient chemotherapy [4]. In autopsy studies, the rate of deep vein thrombosis (DVT) or pulmonary embolism (PE) among cancer patients approximates 50% [5]. Moreover, VTE is a significant predictor of mortality in cancer patients [6–8].

Added to cancer-related mechanisms, cancer therapy, including administration of prothrombotic chemotherapeutic drugs, use of central venous catheters, major surgery, and prolonged immobilization, further increases the risk of VTE [9, 10]. Patients with cancer undergoing surgery have a twofold increase in the risk of VTE in comparison to patients without cancer undergoing similar procedures [11, 12], and the risk persists beyond hospital discharge [13–15]. Moreover, the risk of VTE is doubled in patients with metastatic disease or those undergoing chemotherapy, compared with patients with localized cancer or patients without chemotherapy [16].

Several randomized controlled trials confirmed that thromboprophylaxis among cancer patients safely prevents VTE, with a 45%–68% reduction in relative risk of VTE compared with placebo [17–21]. Therefore, current consensus guidelines of the American College of Chest Physicians [22] and the American Society of Clinical Oncology [23] recommend prophylaxis in acutely ill medical patients with cancer or patients undergoing major cancer surgery (grade 1A).

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We investigated thromboprophylaxis and its predictors before the onset of acute VTE in hospitalized cancer patients.

methods

patients

Overall, 257 consecutive cancer patients with objectively confirmed acute DVT or PE and hospitalization within 30 days before the onset of acute VTE in four academic and 10 nonacademic acute care hospitals in Switzerland were enrolled in the prospective SWIss Venous ThromboEmbolism Registry (SWIVTER) from 1 April 2006 to 31 March 2008. Inclusion criteria were age ≥18 years and hospitalization for an acute illness within 30 days before acute VTE event (medical patients) or hospitalization with trauma or surgery within 30 days before the onset of acute VTE (surgical patients). The only exclusion criterion was hospitalization for acute VTE within 30 days before the enrollment. Patients were classified as inpatients if VTE was diagnosed during hospitalization, and they were classified as outpatients if VTE was diagnosed within 30 days after a hospitalization. Eligible patients were enrolled during clinical inpatient or outpatient visits or at the time of VTE diagnosis. DVT had to be objectively confirmed with ultrasound or phlebography and PE by contrast-enhanced chest computed tomography, ventilation perfusion scan, conventional pulmonary angiography, or magnetic resonance imaging. The detailed methodology of SWIVTER has been described elsewhere [24].

data and statistical analysis

The Geneva risk score was used for an objective assessment to identify patients at high risk for VTE [25]. According to this score, thromboprophylaxis is indicated in patients with a score ≥3 points. Two points are reserved for the following risk factors: cardiac failure, respiratory failure, recent stroke, recent myocardial infarction, acute infectious disease (including sepsis), acute rheumatic disease, cancer, myeloproliferative syndrome, nephrotic syndrome, prior VTE, and known hypercoagulable state; one point is reserved for the following risk factors: immobilization >3 days, recent travel >6 h, age >60 years, body mass index >30 kg/m^2, chronic venous insufficiency, pregnancy, hormonal therapy, and dehydration.

Continuous variables with a normal distribution are described as means with standard deviations, and group comparisons were carried out with the *t*-test; continuous variables with skewed distribution are presented as median values with interquartile ranges, and group comparisons were carried out with a rank sum test. Discrete variables are presented as frequencies and percentages, and group comparisons were carried out using the chi-square or Fisher's exact test. Bonferroni's correction for multiple group comparisons indicated a P value <0.002 for statistical significance. Univariate logistic regression analysis reporting odds ratios with 95% confidence intervals was conducted to identify clinical predictors for the use of prophylaxis within 30 days before the onset of VTE. Then, multivariate logistic regression analysis was carried out to identify independent clinical predictors of prophylaxis within 30 days before the onset of VTE. Univariate predictors with a P value <0.05 were included in the regression model; and a stepwise backward variable elimination procedure was used for obtaining the final multivariate regression model. All reported P values are two tailed. Data were analyzed using STATA 9 software (STATACorp LP, College Station, TX).

results

patient characteristics

Among the 257 enrolled patients, 49% were women, and mean age was 61 ± 15 years. The median duration of hospital stay before the onset of acute VTE was 16 days (interquartile range 8–27 days). Overall, 234 (91%) patients were at high risk (Geneva VTE risk score ≥3), 171 (66%) had metastatic cancer, 136 (53%) were immobile for >3 days, 116 (45%) had recent and 111 (43%) ongoing chemotherapy, 103 (40%) had surgery within 30 days, 91 (35%) had an indwelling central line, 62 (24%) were admitted to the intensive care unit (ICU) within 30 days, 43 (17%) had prior DVT, and 27 (11%) prior PE (Table 1). DVT alone was diagnosed in 102 (40%), acute PE in 99 (38%), and PE plus DVT in 56 (22%) patients. Among patients with acute DVT with or without PE, 155 (70%) had proximal, 93 (42%) distal, and 25 (11%) upper extremity vein thrombosis. At the time of VTE diagnosis, 199 (77%) were inpatients and 58 (23%) were outpatients. A Geneva VTE risk score ≥3 was present in 94% of the inpatients and in 84% of the outpatients during the preceding hospitalization ($P = 0.022$).

In total, 19 (7%) patients died within 7 days after VTE diagnosis: VTE was the main cause of death in 10 (53%) of these patients, and VTE likely contributed to death in 15 (79%).

type of VTE prophylaxis within 30 days before the onset of VTE

Overall, 153 (60%) patients received thromboprophylaxis before the acute index VTE; among the 144 medical patients, 69 (48%) received prophylaxis, and among the 113 surgical or trauma patients, 84 (74%) received prophylaxis ($P < 0.001$). In total, pharmacological prophylaxis was used in 125 (49%) patients and mechanical methods in 53 (21%). Among the patients with pharmacological prophylaxis, 92 (74%) received low-molecular weight heparin; the median dose for dalteparin was 5000 IU, for enoxaparin 4000 IU, and for nadroparin 2850 IU. Unfractionated heparin was used in 21 (16%) patients, and 18 (14%) patients were on vitamin K antagonists before the onset of VTE. Combined mechanical plus pharmacological prophylaxis was used in 25 (10%) patients. Among the 153 patients with prophylaxis, it was stopped before the onset of VTE in 27 (18%) patients with a median prophylaxis suspension time of 9 days (interquartile range 4–14 days).

Among the 104 patients without prophylaxis, 88 (85%) had a Geneva VTE risk score ≥3. The proportion of patients with prophylaxis according to the Geneva VTE risk score is shown in Figure 1. Among the 111 patients with ongoing chemotherapy, 56 (50%) received VTE prophylaxis, and among the 103 patients undergoing surgery for cancer, 79 (77%) received prophylaxis. Thromboprophylaxis within 30 days was more frequently used in inpatients ($n = 133$; 67%) than in outpatients ($n = 20$; 34%) ($P < 0.001$).

Among the 144 medical patients, 84 (58%) had ongoing chemotherapy and 115 (80%) metastatic cancer. There was no difference in the rate of thromboprophylaxis between the medical patients with and without ongoing chemotherapy (45% versus 55%, respectively; $P = 0.45$). There was no difference in the rate of thromboprophylaxis between the medical patients with and without metastatic cancer (50% versus 50%, respectively; $P = 0.23$).

Table 1. Patient demographics, chronic and acute comorbidities

	Total, $N = 257$	Prophylaxis, $n = 153$	No prophylaxis, $n = 104$	P
Demographics				
Age, years, mean ± SD	61.5 ± 15.1	61.1 ± 15.3	62.2 ± 14.8	0.58
Women, *n* (%)	127 (49.4)	75 (49.0)	52 (50.0)	0.88
Chronic comorbidities				
Metastatic cancer, *n* (%)	171 (66.5)	100 (65.4)	71 (68.3)	0.63
Chemotherapy within 6 months, *n* (%)	116 (45.1)	59 (38.6)	57 (54.8)	0.013
Cancer surgery within 6 months, *n* (%)	77 (26.1)	49 (32.0)	28 (26.9)	0.39
Radiotherapy within 6 months, *n* (%)	46 (17.9)	25 (16.3)	21 (20.2)	0.44
Prior DVT, *n* (%)	43 (16.7)	36 (23.5)	7 (6.7)	<0.001
Chronic lung disease, *n* (%)	33 (12.8)	23 (15.0)	10 (9.6)	0.20
Neurological disorder, *n* (%)	28 (10.9)	17 (11.1)	11 (10.6)	0.89
Prior PE, *n* (%)	27 (10.5)	22 (14.4)	5 (4.8)	0.014
Obesity, *n* (%)	15 (5.9)	12 (7.8)	3 (2.9)	0.096
Thrombocytopenia, *n* (%)	12 (4.7)	4 (2.6)	8 (7.7)	0.058
Congestive heart failure, *n* (%)	11 (4.3)	9 (5.9)	2 (1.9)	0.12
Renal failure, *n* (%)	11 (4.3)	8 (5.2)	3 (2.9)	0.36
Liver disease, *n* (%)	11 (4.3)	6 (2.1)	5 (4.8)	0.73
Varicous veins, n (%)	7 (2.7)	5 (3.3)	2 (1.9)	0.52
Acute comorbidities <30 days				
Bed rest >3 days, *n* (%)	136 (52.9)	94 (61.4)	42 (40.4)	0.001
Ongoing chemotherapy, *n* (%)	111 (43.1)	56 (36.6)	55 (52.9)	0.010
Surgery, *n* (%)[a]	103 (40.0)	79 (76.7)	24 (23.3)	<0.001
Indwelling central line, *n* (%)	91 (35.4)	70 (45.8)	21 (20.2)	<0.001
Nonpulmonary infection, *n* (%)	63 (24.5)	43 (28.1)	20 (19.2)	0.11
ICU admission, *n* (%)	62 (24.1)	57 (37.2)	5 (4.8)	<0.001
Pulmonary infection, *n* (%)	31 (12.1)	19 (12.4)	12 (11.5)	0.83
Bleeding, *n* (%)	31 (12.1)	20 (13.1)	11 (10.6)	0.55
Acute respiratory failure, *n* (%)	26 (10.1)	17 (11.1)	9 (8.7)	0.52
Sepsis, *n* (%)	21 (8.2)	14 (9.2)	7 (6.7)	0.49
Ischemic stroke or palsy, *n* (%)	19 (7.4)	17 (11.1)	2 (1.9)	0.006
Dehydration, *n* (%)	14 (5.5)	16 (4.9)	6 (5.8)	0.85
Trauma, *n* (%)	12 (4.7)	7 (4.6)	5 (4.8)	0.93
Acute heart failure, *n* (%)	10 (3.9)	7 (4.6)	3 (2.9)	0.49
Acute coronary syndrome, *n* (%)	3 (1.2)	3 (2.0)	0 (0.0)	0.15
Acute rheumatic disease, *n* (%)	3 (1.2)	2 (1.3)	1 (1.0)	0.80
Hospital days, median (IQ range)	16 (8–27)	19 (11–29)	10 (4–24)	<0.001
Hospital stay >15 days, *n* (%)	137 (53.3)	94 (61.4)	43 (41.4)	0.002
Mortality at 7 days, *n* (%)	19 (7.4)	15 (9.8)	4 (3.9)	0.073

[a]some patients had more than one surgical procedure.

SD, standard deviation; DVT, deep vein thrombosis; PE, pulmonary embolism; ICU, intensive care unit; IQ, interquartile.

predictors of VTE prophylaxis before the onset of acute VTE

The strongest univariate predictors of prophylaxis were ICU admission within 30 days, surgery within 30 days, and use of an indwelling central catheter (Table 2). Outpatient status at the time of VTE diagnosis, ongoing chemotherapy, and recent chemotherapy were univariately associated with the absence of VTE prophylaxis.

In multivariate analysis, ICU admission, prior DVT, surgery within 30 days, bed rest >3 days, and outpatient status at the time of VTE diagnosis remained the only clinical factors that independently predicted the use of prophylaxis (Table 3).

discussion

The present analysis from the SWIVTER showed that only 60% of cancer patients hospitalized for an acute medical illness or surgery within 30 days before the index VTE event were receiving thromboprophylaxis at the time of onset. This finding is consistent with the results of observational studies confirming that a large proportion of hospitalized patients do not receive prophylaxis before the VTE event [24–26].

In our study, the prophylaxis rate before VTE in the medical inpatients with cancer was similar (48%) to that of the multinational International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) registry (45%) [27]. In the Spanish Registro Informatizado de la Enfermedad

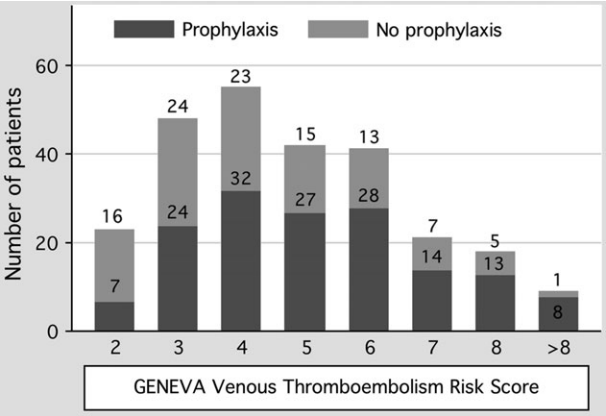

Figure 1. Venous thromboembolism prophylaxis in cancer patients according to the GENEVA risk score.

Table 2. Univariate clinical predictors of prophylaxis in patients with cancer

Predictor	OR	95% CI	*P*
ICU admission	11.76	4.52–30.59	<0.001
Surgery within 30 days	3.56	2.04–6.20	<0.001
Indwelling central line	3.33	1.88–5.92	<0.001
Ischemic stroke or palsy within 30 days	2.52	1.20–5.31	0.015
Bed rest >3 days	2.35	1.41–3.91	0.001
Hospital stay >15 days	2.26	1.36–3.76	0.002
Prior DVT	2.06	1.35–3.16	0.001
Prior PE	1.82	1.10–3.01	0.019
Chemotherapy within 6 months	0.53	0.32–0.88	0.014
Ongoing chemotherapy	0.51	0.31–0.85	0.010
Outpatient at the time of VTE diagnosis	0.31	0.18–0.53	<0.001

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 3. Independent clinical predictors of prophylaxis in patients with cancer

Predictor	OR	95% CI	*P*
ICU admission	7.02	2.38–20.68	<0.001
Prior DVT	3.48	2.14–5.64	<0.001
Surgery within 30 days	2.43	1.19–4.99	0.015
Bed rest >3 days	2.02	1.08–3.79	0.028
Outpatient at the time of VTE diagnosis	0.38	0.19–0.76	0.006

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; DVT, deep vein thrombosis; VTE, venous thromboembolism.

TromboEmbolica (RIETE) registry, 24% of the medical and 71% of the surgical cancer inpatients received thromboprophylaxis before the onset of acute VTE [28]. Of note, SWIVTER included a higher proportion (45%) of cancer patients than the RIETE (13%) and the IMPROVE (12%) registries [24].

In the present study, almost one-quarter (23%) developed VTE as outpatients shortly after a hospitalization, confirming that cancer patients have an ongoing risk of VTE beyond the hospital stay [13–15]. In outpatients with cancer, VTE prophylaxis is currently not recommended by international consensus guidelines and not reimbursed in many countries. Not surprisingly, we found that outpatient diagnosis of VTE independently predicted absent prophylaxis. Further studies are required to investigate whether thromboprophylaxis should be recommended in cancer outpatients at high risk of VTE.

The majority of our cancer population had additional VTE risk factors, including ongoing chemotherapy, metastatic disease, recent surgery, indwelling central venous catheter, or a personal history of VTE. Thus, >90% of patients had an indication for prophylaxis according to the Geneva risk score [25]. An increased risk of bleeding before the onset of VTE may partially explain the omission of pharmacological thromboprophylaxis. The proportion of patients with thrombocytopenia was rather low (5%), and not surprisingly, we found a strong trend toward nonprescription of prophylaxis in those patients. However, there is no reason to withhold mechanical thromboprophylaxis in cancer patients with an increased risk of bleeding.

In SWIVTER, we investigated clinical predictors of thromboprophylaxis [24]. Several known VTE risk factors, such as ICU admission, surgery within 30 days, bed rest >3 days, and prior DVT independently predicted the use of prophylaxis. We were surprised by the finding that none of the other important VTE risk factors, including age, obesity, and metastatic disease, and none of the acute comorbidities, including acute heart failure, respiratory failure, and infections, were predictive for prophylaxis. Additionally, the finding that both recent and ongoing chemotherapy were associated with the absence of prophylaxis is troublesome. In a recent study of outpatients with chemotherapy-related VTE, the site of cancer, an increased platelet count, a hemoglobin level of <100 g/l or use of red cell growth factors, an increased leukocyte count, and the presence of obesity predicted VTE [29].

Potential explanations for the observed underuse of VTE prophylaxis in cancer patients may include an increased risk of bleeding, use of chemotherapeutic drugs affecting angiogenesis, presence of transient chemotherapy-induced thrombocytopenia, reduced quality of life through daily injections, or cost–benefit concerns. In addition, patients with end-stage disease usually do not receive thromboprophylaxis; however, the proportion of patients with terminal cancer was probably not substantial in our analysis because of a low overall in-hospital mortality rate (7%).

The strength of the present study is the prospective multicentric enrollment of consecutive cancer patients who developed acute VTE during or shortly after hospitalization with detailed information on VTE risk factors, comorbidities, and prophylaxis modalities. A weakness of the study is that no information on type of cancer or type and duration of chemotherapy was collected. Another study limitation is the use of the nonvalidated Geneva VTE risk score. However, it is unlikely that the observed rate of appropriate prophylaxis would have changed significantly by the use of another risk score because the proportion of patients with multiple VTE risk factors was substantial.

The present data—together with the findings from the RIETE and IMPROVE registries—confirm that there is a definite need

to improve prophylaxis in cancer patients. Several quality improvement activities, such as electronic or human alerts [30], continuing medical education [31], hospital prophylaxis guidelines, or VTE risk assessment models may improve prophylaxis and should be implemented systematically in institutions who care for cancer patients.

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disclosures

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